

VU Research Portal

Circadian rhythm disturbances in end-stage renal disease

Russcher, M.

2015

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Russcher, M. (2015). *Circadian rhythm disturbances in end-stage renal disease*. [PhD-Thesis – Research external, graduation internal, Vrije Universiteit Amsterdam].

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

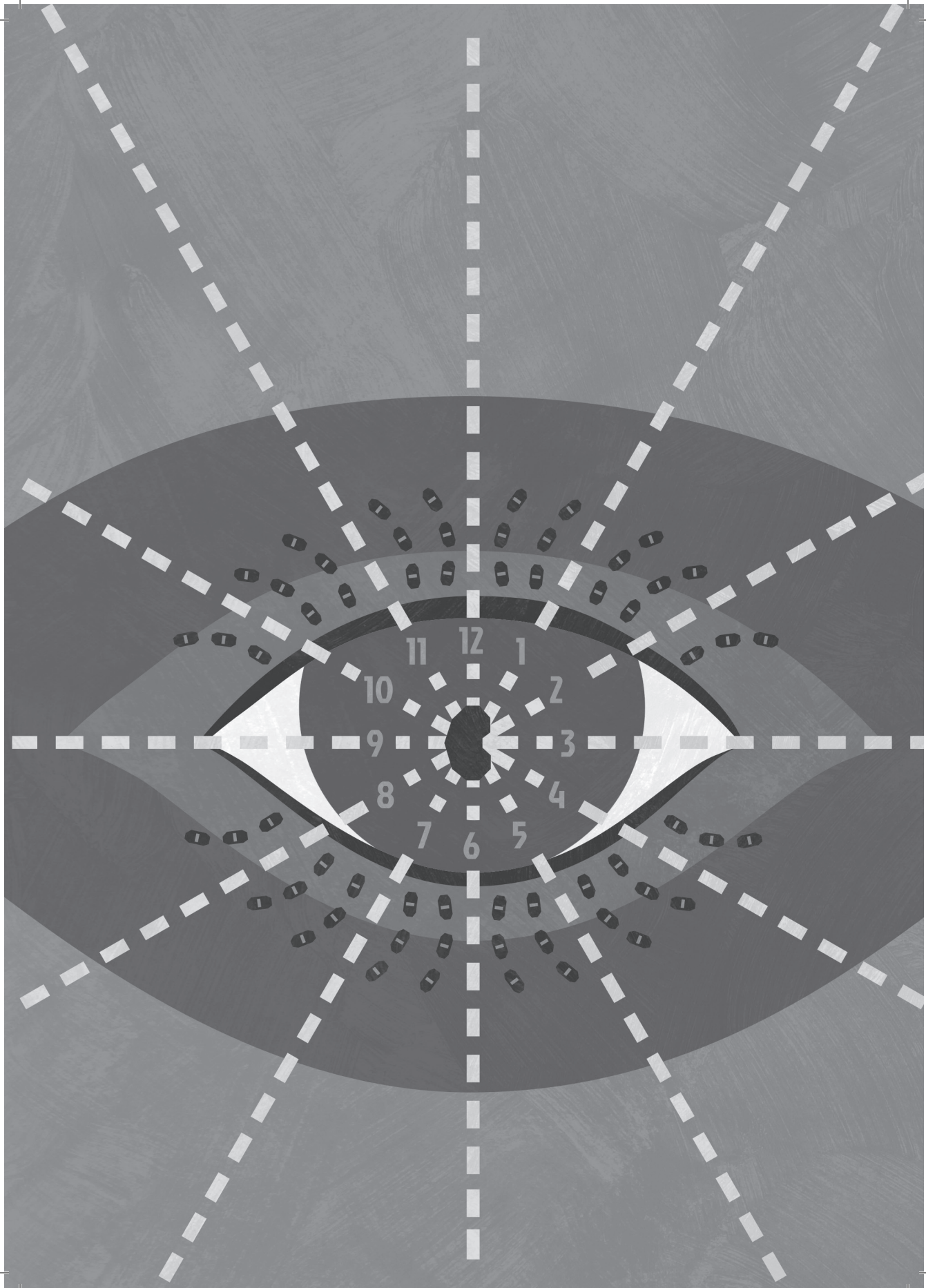
- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

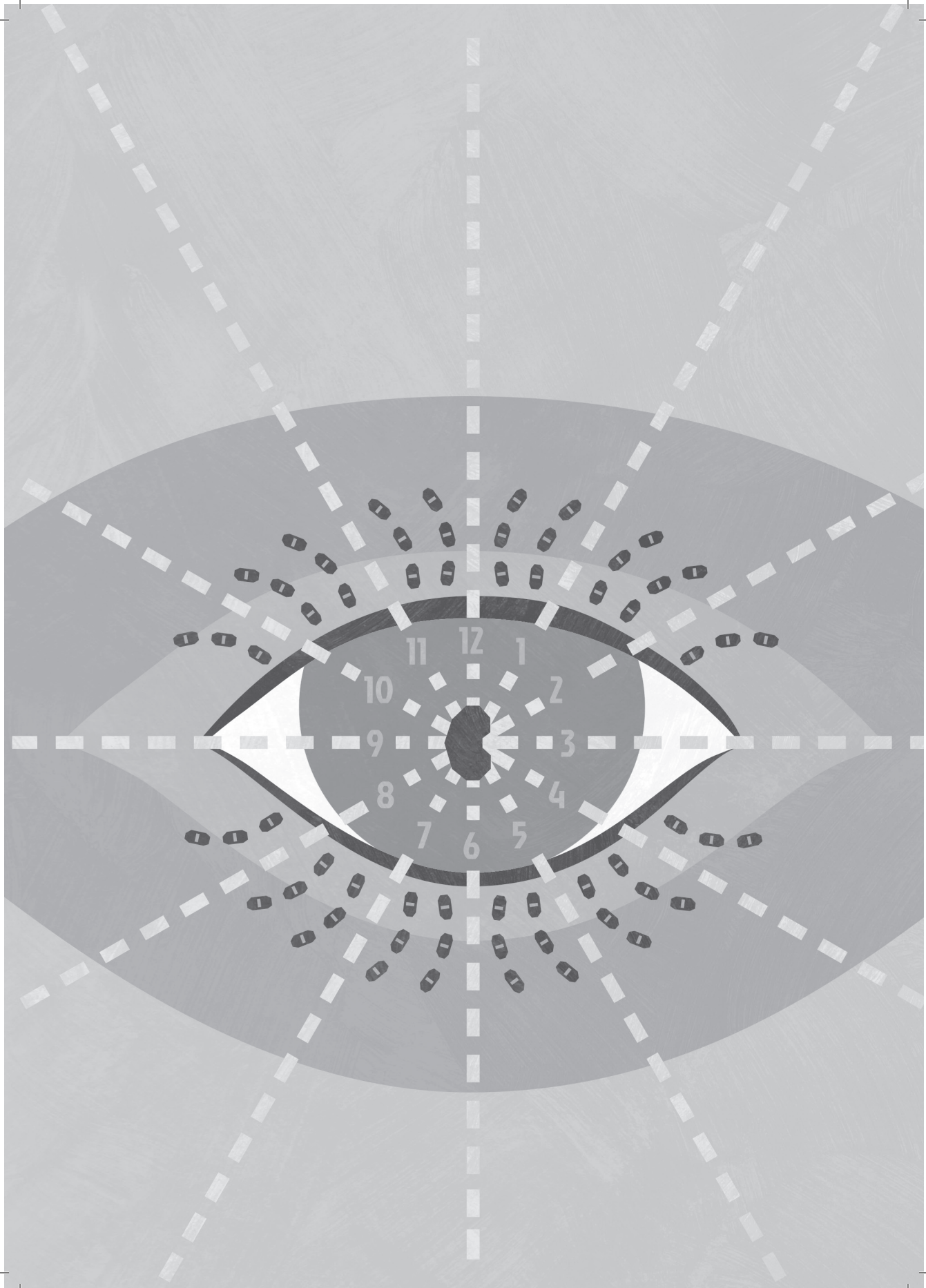
vuresearchportal.ub@vu.nl





Part I

Background information



Chapter 1

General introduction



Introduction

Chronic kidney disease (CKD) is a global public health problem. In 2007, it was estimated that 9.6% of adults suffered from CKD. It is associated with other chronic illnesses, such as hypertension and diabetes. Patients with CKD have a reduced life expectancy and are especially at risk for cardiovascular morbidity and mortality.(1) In addition, their quality of life is severely decreased.(2) One of the aspects that affects quality of life negatively, is the frequent occurrence of sleep problems in this population, especially in patients with end-stage renal disease (ESRD).(3,4) Sleep disturbances have different etiologies. In this thesis, we question whether a disturbance in circadian timekeeping, i.e. maintaining stable 24-hour rhythms of bodily functions, is one of the underlying causes of sleep complaints in ESRD patients. Research has shown that patients with end-stage renal disease suffer from disturbances in circadian rhythms. For example, the normal 24-hour rhythm in blood pressure with higher daytime values and lower nighttime values often is disrupted in kidney patients.(5) Also the involvement of the circadian clock within the kidney in generating 24-hour renal rhythms, such as urine formation and excretion, has received research attention.(6,7) In this thesis, different aspects of disturbed circadian rhythmicity in kidney patients are discussed: the origin, the association with renal function and targets for treatment. This first chapter provides background information on these aspects and a general outline of the contents of this thesis.

Definition of chronic kidney disease

The National Kidney Foundation Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has defined chronic kidney disease (CKD) as follows: abnormalities of kidney structure or function which have been present for at least 3 months and have implications for health. Examples of kidney damage are persistent albuminuria, urine sediment or electrolyte abnormalities, abnormalities visible with histology or imaging of the kidney or a history of kidney transplantation. Decreased glomerular filtration rate (GFR) may or may not be present. Without other signs of kidney damage, CKD can be defined by a GFR <60 ml/min/1.73m² for three or more months.

Classification of CKD is based on Cause, GFR category and Albuminuria (CGA staging). As to the cause of CKD, primary kidney disease, in which the disease is restricted to the kidney, is distinguished from systemic disease. Hypertension, diabetes mellitus and vascular disease are examples of the latter type of cause of CKD. In addition, if known,

the location of the disease within the kidney should be listed. Concerning GFR, five categories are specified, ranging from G1 (normal or high GFR >90 ml/min/1.73m²) to G5 (GFR <15 ml/min/1.73m²). In case of stage G5, kidney failure, often some form of renal replacement therapy, i.e. dialysis or kidney transplantation, is required. Albuminuria is categorized in three levels: A1 (normal to mildly increased, urine albumin-to-creatinine ratio (ACR) <30 mg/g) to A3 (severely increased, ACR >300 mg/g).

CKD can be an irreversible progressive loss of renal function with a life-long course, especially in hypertensive patients and persistent proteinuria >1 g/day, but progression of CKD can also be halted either spontaneously or with treatment. The prognosis of CKD is associated with CGA stage, other risk factors and comorbid conditions. Patients with CKD are at higher risk to develop cardiovascular disease, end-stage renal disease, acute kidney injury and progression of CKD. Patients with severe loss of kidney function (CKD stages 4 and 5) develop anemia, bone and mineral disorders and acid-base disorders.(8)



Sleep disturbances in chronic kidney disease

Previous research has shown that between 30% and 80% of individuals with ESRD report subjective sleep-related problems, ranging from insomnia to periodic limb movement disorder.(9–12) It is unknown to what extent circadian rhythm disorders are the underlying cause of the sleep problems in ESRD patients.

Patients on daytime hemodialysis and patients with CKD both have reduced total sleep time and reduced sleep efficiency in comparison with healthy subjects.(13) Total sleep time indicates the total number of minutes that a person actually sleeps during the night. Sleep efficiency is the total sleep time divided by the time spent in bed. Compared with patients with CKD, hemodialysis patients have in addition to reduced total sleep time, less rapid eye movement sleep, a higher brief arousal index, a higher respiratory disturbance index, less total sleep time, increased number of wake minutes after initial sleep onset, lower sleep efficiency, a higher periodic limb movement index and longer sleep onset latencies, which means their sleep is even more affected.(13) These findings might also suggest that there are additional factors that have a negative influence on sleep in hemodialysis patients. Functional and psychological factors might have a role in patients with CKD, in addition hemodialysis patients suffer from intrinsic sleep disruption (e.g. arousal, apnea and limb movements) secondary to the effects of intermittent daytime hemodialysis treatment.(13)

Factors that might cause sleep disturbances in chronic kidney disease

In patients with ESRD, sleep can be disturbed by both intrinsic factors, e.g. metabolic changes, and extrinsic factors, e.g. dialysis treatment, and the use of medications (reviewed in (14)).

The hemodialysis treatment procedure

Daytime hemodialysis can increase daytime sleep propensity and daytime napping, which might lead to delayed sleep onset at night and decreased nighttime sleep. Several possible causes for this dialysis-associated sleepiness exist.

Firstly, body temperature often rises during HD treatment. Although mechanisms are still not completely elucidated, one of the causes could be cytokine production by mononuclear cells (interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)) influenced by complement activation, interaction with the dialyzer and/or exposure to bacterial wall fragments.(15–17) Cytokines are recognized as a pyrogenic signal within the central nervous system, leading to a rise in body temperature. Intra-dialytic changes in body temperature also appear to follow the endogenous diurnal temperature rhythm, which provides an additional explanation for the increase in body temperature during dialysis. A higher rise is seen in morning hemodialysis shifts than in afternoon shifts.(18)

In reaction to the hemodialysis-associated elevations in body temperature, the body might activate cooling mechanisms. There is a known association between internal body cooling and sleep onset.(19,20) This might enhance daytime sleep propensity, particularly during the post-hemodialysis period. Chronic, episodic elevations in body temperature in association with recurrent hemodialysis treatments might therefore alter the sleep propensity rhythm.(21)

Also, the hemodialysis procedure is a significant physical and psychological stressor. The stress response triggered by emotional arousal can lead to reactions such as anxiety, depression and increased daytime sleepiness.(22,23)

Finally, hemodialysis may also affect the sleep–wake cycle by altering exposure to *Zeitgebers* (time cues) that help set or entrain the circadian system. The time of day that treatment is given can affect an individual's wake-up time, time for physical activity, meal times, light exposure and social activities.(24)

Medication

Because of the high prevalence of sleep problems, 39% of hemodialysis patients use sleep inducing medications, such as benzodiazepines, benzodiazepine receptor agonists zolpidem and zopiclon, the neuroleptic antihistamine promethazine, antidepressant mirtazapine and melatonin. Of these, benzodiazepines are most commonly prescribed. About one third of hemodialysis patients are prescribed benzodiazepines, compared to 15% of the general Dutch population.(25) The advantage of benzodiazepine use in treating insomnia is their increasing effect on total sleep time and reduction of sleep onset latency. Sleep quality, however, is not improved since benzodiazepines suppress rapid eye movement (REM) and slow-wave sleep.(26) Benzodiazepines can reduce sleep quality since they worsen sleep apnea by reducing tension of the upper respiratory muscles and dampening the physiological reaction to hypercapnia.(27,28) Benzodiazepines may also decrease nocturnal melatonin production.(29) The role of decreased melatonin levels in ESRD is discussed later in this chapter. Benzodiazepines have been shown to have minimal efficacy in the general older population with sleep problems.(30)

Other medications can influence sleep as well. Examples of drug classes are antidepressants, anti-epileptic drugs and medication against Parkinson's Disease. Most notably hemodialysis patients use more antihypertensive β -adrenergic-receptor antagonists (beta-blockers) than the general Dutch population. Fifty-six percent of hemodialysis patients use beta-blockers compared with 12 percent of the general Dutch population. (25) Beta-blockers have been associated with tiredness, insomnia, nightmares and vivid dreams, depression, mental confusion and psychomotor impairment.(31,32) The severity of adverse effects is affected by the age of the patient and the administered dose: older patients are more sensitive to medication because of altered absorption and metabolism of drugs in older age. In general, sleep disturbances seem to be more common with lipophilic beta-blockers, e.g. metoprolol than with hydrophilic beta-blockers, e.g. atenolol. However, even atenolol, the most hydrophilic beta-blocker available, has been shown to increase total wake time at night.(32) In addition, beta-blockers decrease nocturnal melatonin release via inhibition of adrenergic beta1-receptors.(33)

Another class of antihypertensive drugs, the calcium channel antagonists, may also lower nocturnal melatonin secretion. In vitro research has shown that nifedipine reduced melatonin production in rat pineal cells.(34) However, this effect of nifedipine could not be shown in a human in vivo study.(35)

Finally, glucocorticosteroids influence sleep negatively. They are often used, e.g. after kidney transplantation. Sleep disturbances are a frequently reported side-effect. This seems to be dose-related.(36)



Metabolic changes

Excessive daytime sleepiness in patients with ESRD might be related to, amongst others, uremia. The blood urea nitrogen level is significantly higher in patients on conventional hemodialysis with pathological daytime sleepiness than in 'alert' patients.(37,38) In addition, sleep onset latency is negatively correlated with blood urea nitrogen level.(38) In a study on subjective sleep efficiency within hemodialysis patients, Koch *et al.* found an association between decreased sleep efficiency and increased phosphate and urea.(39) However, the results of earlier studies in patients on hemodialysis investigating possible associations between biochemical parameters and sleep disturbances show conflicting results. One study showed serum phosphate levels to correlate inversely with sleep disturbances (40), but another study showed that only urea had a significant relationship with sleep disturbances.(9) Other researchers found no correlations at all between biochemical markers and sleep disturbances.(10)

Hemoglobin levels between 10 and 12 g/dl were associated with better sleep efficiency.(39) Erythropoietin deficiency seems to play a role in dysregulation of melatonin metabolism in chronic renal failure.(41) However, the precise role of erythropoietin in melatonin metabolism in renal failure, the existence of its circadian rhythm (42–45) and its relationship with melatonin needs further investigation.

Melatonin and chronic kidney disease

The neurochemical agent melatonin (N-acetyl-5-methoxytryptamine) is synthesized from tryptophan, transformed to serotonin and then converted to melatonin, principally by the pineal gland (figure 1).

Its secretion shows a clear rhythm with low daytime levels and high nighttime levels with maximum plasma levels around 03:00-04:00 a.m.. The liver, which clears more than 90% of circulating melatonin, is the primary site for metabolism. Melatonin is first hydroxylated, then sulphated or to a lesser extent glucuronidated and excreted in the urine.(46)

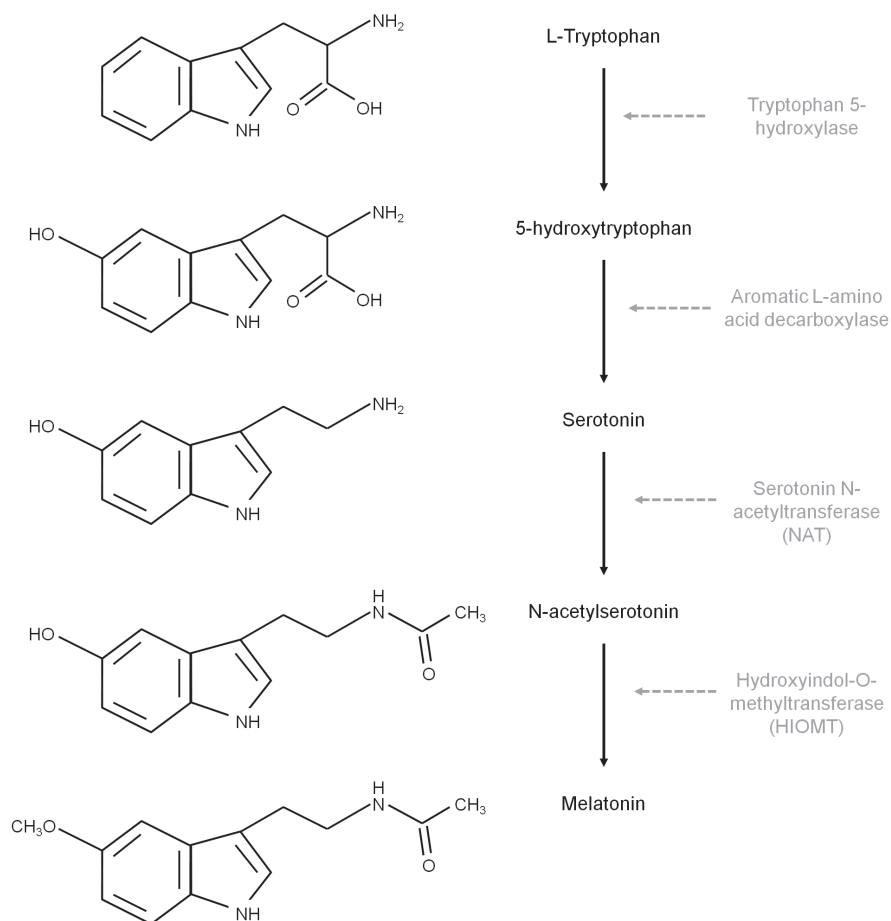


FIGURE 1. Synthesis pathway of melatonin

The two rate-limiting enzymes in melatonin synthesis are Serotonin-N-acetyltransferase (NAT) and Hydroxyindol-O-methyltransferase (HIOMT)

The rhythm of melatonin secretion is recognized as the most robust signal available for studying circadian rhythms in humans.(47) Its rhythm is generated under the influence of the light/dark cycle by the endogenous clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus in the brain. Light information is transmitted to the SCN via retinohypothalamic fibers. The subsequent signal of the SCN travels onwards through the cervical sympathetic ganglia, then projects on the pineal gland where melatonin is synthesized. The presence of light inhibits melatonin production in the pineal during daytime (figure 2).

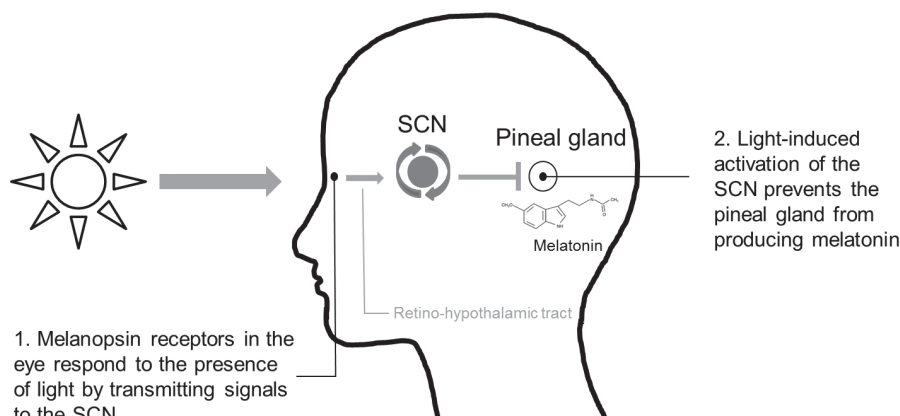


FIGURE 2. Melatonin secretion by the pineal gland under the influence of the SCN

Melatonin itself plays an important role in giving time cues to the body. It is the 'hormone of darkness', it signals the 'biological night'. When melatonin concentrations rise, this is interpreted by the body as the start of the 'night phase'. Melatonin is sometimes falsely referred to as the 'sleep hormone'. In humans, through indirect effects, melatonin is indeed involved in sleep-wake regulation. As for humans the biological night corresponds to the rest phase, an increase of melatonin correlates with sleep propensity and onset of sleep.(48) However, in nocturnal animals which are active during the night melatonin marks the start of the active phase. In that sense, melatonin does not appear as the universal hormone of sleep, but acts as an endogenous synchronizer able to stabilize circadian rhythms, to reinforce these rhythms and maintain phase relationships between different circadian rhythms.(46)

The onset of melatonin production, measured under dim-light conditions in serum or saliva (dim-light melatonin onset; DLMO), is used as a marker of an individual's circadian phase. The DLMO can be calculated as the first interpolated point above 10 pg/ml in serum after which the melatonin concentration continues to rise.(49)

Remarkably, studies on patients with CKD, patients on daytime hemodialysis and animal models of CKD have shown that the nocturnal surge in melatonin above the DLMO is absent in CKD.(41,50–53) A relationship between decreasing renal function and decreased concentrations of melatonin was found. The cause of the decline in melatonin levels in patients with CKD is unknown, but could be the result of an impairment in beta-adrenoreceptor-mediated responsiveness.(51,54) Plasma from uremic hemodialysis patients decreases the number of β_1 - and β_2 -adrenoreceptors significantly

in vitro, compared with plasma from healthy controls.(55) The adrenergic system plays an important role in the synthesis of N-acetyltransferase (NAT) (56), a rate limiting and key enzyme in melatonin biosynthesis, see figure 1. Nocturnal levels of NAT activity are decreased at least in rats rendered uremic by partial nephrectomy.(57) Impairment in adrenergic function is associated with the decline in melatonin levels in patients with CKD.(52)



Although a direct correlation between nocturnal melatonin levels and sleep quality has not been established, it is known that melatonin reinforces the nocturnal decrease of central body temperature which facilitates sleep propensity. There is a clear relationship between the duration of sleep and melatonin secretion. Suppressed melatonin levels due to nighttime light exposure enhances alertness immediately.(46) Therefore the low melatonin levels in HD patients may lead to reduced sleep stimuli. Administration of exogenous melatonin to HD patients has shown short-term beneficial effects on sleep.(58)

Circadian rhythms and the human circadian clock

An endogenous clock, known as the biological or *circadian* clock drives bodily functions that recur in a cycle of about 24 hours. 'Circadian' derives from the Latin *circa dies*, which roughly translates to 'approximately a day'. These intrinsic rhythms stay present with a near-to-24-hour period even in constant conditions without time cues from the environment. Endogenous biological clocks are fundamental to all living organisms. They enable the organism to anticipate and adapt to daily recurring changes in the environment.(6,59) A schematic representation of the circadian system has three components: an input pathway for time cues, the clock itself which generates 24-h oscillations and synchronizes rhythms to the input signals and an output pathway that translates the clock rhythms to time dependent biochemical, physiological and behavioral processes (see figure 3).

In mammals, the circadian clock is organized in a hierarchy of multiple oscillators. The central clock at the top of the hierarchy is located in the suprachiasmatic nuclei (SCN) in the hypothalamus in the brain. The SCN pacemaker provides a crucial link between the outside world and the internal circadian time-keeping mechanism. The SCN itself receives clock-resetting environmental information to keep synchronized, or *entrained*, with the earth's 24-h light-dark cycle. The main environmental cue that serves as a Zeitgeber ('time giver') is light. Light information is sent to the SCN from the eye via the retino-hypothalamic tract.(61) In addition to the SCN, there are peripheral clocks in virtually all other cells and tissues.(62) These peripheral oscillators have self-sustaining

circadian rhythmicity, but without central control they run out of phase. To keep them in phase, they are synchronized by timing cues (outputs) from the central SCN pacemaker through humoral and neuronal signals.(62,63) In addition, peripheral oscillators can be synchronized by food or metabolic cues, exercise or body temperature (reviewed in (60,64)).

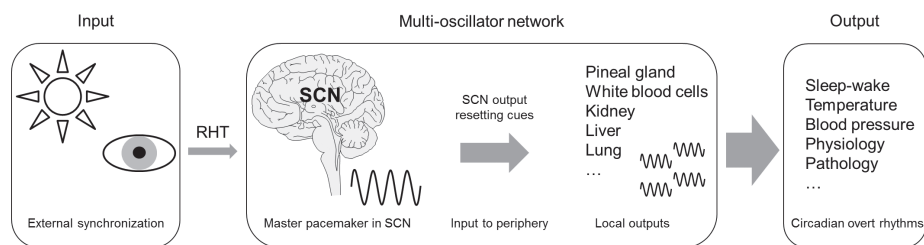


FIGURE 3. The human circadian clock

The circadian clock can be divided in three components: the inputs, the 24-h clock and the outputs. The mammalian clock is organized in a hierarchy of multiple oscillators, in which the SCN is the central pacemaker at the top of the hierarchy. The SCN is synchronized by the external 24-h cycle and in turn coordinates the physiological outputs. The multi-oscillator network is synchronized through multiple lines of communication. For the SCN, light represents the primary input. Peripheral oscillators are reset by timing cues from the SCN (that is, SCN outputs), which regulate local circadian physiology (local outputs). Intercellular synchronization within the SCN is very important for the robust operation of the entire clock. Adapted from: Liu A, Lewis W, Kay S. Mammalian circadian signaling networks and therapeutic targets. *Nat Chem Biol.* 2007;3(10):630–9 (60)

All species share common elements in the molecular design of the circadian oscillator. The core clock is composed of an intracellular molecular oscillator that operates via the basic process of molecular biology: DNA, transcribed to RNA, translated to protein. The oscillator is composed of positive and negative limbs, which form feedback loops (transcription-translation feedback loop, TTFL). In these loops, the positive elements activate the expression of clock genes. The clock genes, as well as driving rhythmic biological outputs, encode negative elements that inhibit the activities of the positive elements. Degradation of the negative elements allows the positive elements to restart the cycle.(65,66) One of the clock genes is *Clock* (*circadian locomotor output cycles kaput*), which codes for the CLOCK protein that is constitutively expressed. It forms a heterodimer with the BMAL1 protein (encoded by *brain and muscle Arnt-like protein-1*, *Bmal1*), together they form the 'positive limb' of the core clock. The CLOCK/BMAL1 heterodimer activates expression of the *Cry* (*Cryptochrome*) and *Per* (*Period*) genes, increasing mRNA levels and consequently PER and CRY protein levels. The CRY and PER proteins in turn inhibit transcriptional activity of CLOCK/BMAL1, abolishing the activation



of *Per* and *Cry* expression and forming the 'negative' limb of the feedback loop. The PER and CRY proteins are then degraded by phosphorylation and so the inhibition of CLOCK/BMAL1 heterodimers subsides, thus allowing the cycle to restart. In addition, there is a second negative feedback loop. CLOCK/BMAL1 also activates transcription of the genes *Rev-Erba*, also known as *nuclear receptor subfamily 1, group D, member 1* (*Nr1d1*) and *Rora* (*retinoic acid receptor-related orphan receptor*). REV-ERB α accumulates quickly and inhibits *Bmal1* transcription, then RORA, which accumulates more slowly, activates *Bmal1* transcription (see figure 4).

Other targets of the core clock proteins are clock controlled genes (CCGs). These are important for translating the core clock rhythms into biochemical, physiological or behavioral rhythms. They for example express humoral factors through which the SCN communicates with peripheral cells.(60)

The circadian rhythm of peripheral cells can be investigated *in vitro* with a bioluminescence technique. A clock reporter-luciferase construct is built into the genome of cells after the promotor region of the reporter clock gene. By adding luciferin, the substrate of luciferase, to the culture medium fluorescence is generated at the moments of clock gene transcription. By recording fluorescence over time, cyclic transcription of the reporter clock gene is revealed.

Unlike SCN cells, peripheral cells don't communicate with each other with regard to circadian rhythm generation. Without centrally driven alignment, the peripheral cells will run out of phase. As a result, oscillations of populations of peripheral cells *in vitro* damp over time, ultimately showing nearly constant expression levels due to self-sustained, but dephased oscillators. An external signal that contains clock resetting factors, e.g. a 'serum shock' (replacement of culture medium with serum), synchronizes these dephased individual oscillators. As a result a cyclic rhythm of fluorescence intensity can be read out (see figure 5).(67) The amplitude of the oscillation reflects the synchronizing capacity of the external signal. In this way, when patients' serum is used, the synchronizing capacity, i.e. the presence of clock resetting factors, can be compared with the synchronizing capacity of healthy control serum by comparing both amplitudes.

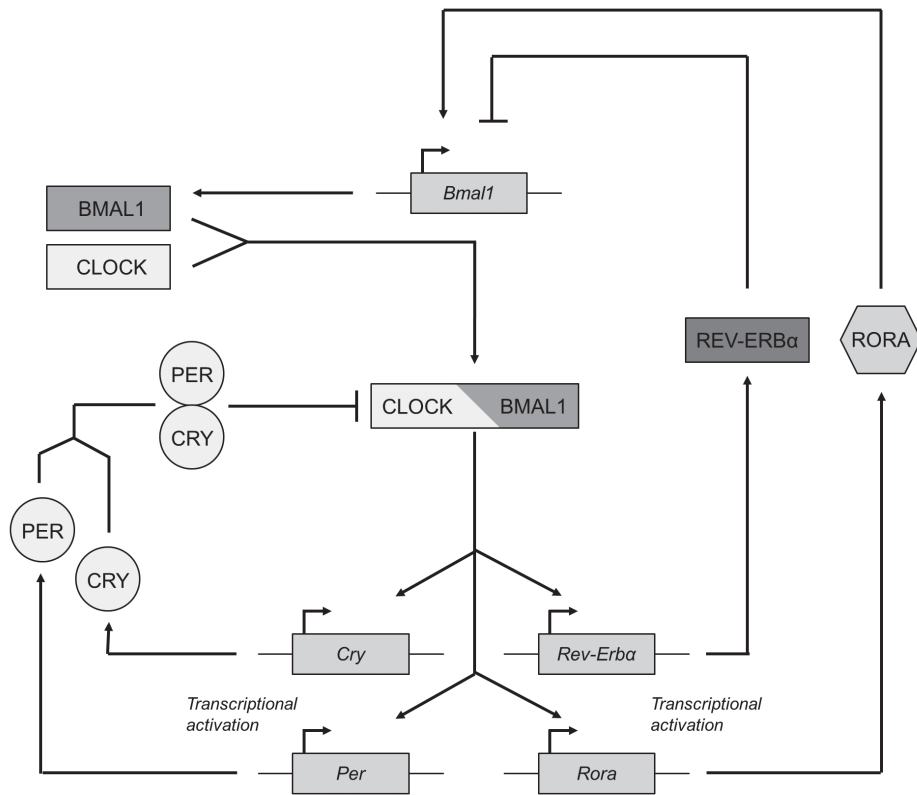


FIGURE 4. Molecular interactions in mammalian circadian-feedback loops

CLOCK and BMAL1 form heterodimers and activate transcription of the genes period (*Per*) and cryptochrome (*Cry*), the retinoic acid receptor-related orphan receptor gene *Rora* and the orphan nuclear receptor REV-ERB group member gene *Rev-Erbα*. PER and CRY proteins slowly accumulate as heterodimers and feed back to inhibit CLOCK-BMAL1 dependent transcription. REV-ERBα accumulates quickly and inhibits *Bmal1* transcription. Then RORA, which accumulates more slowly, activates *Bmal1* transcription. This oscillator is composed of interlocking feedback loops, that regulate the abundance and activity of transcription factors. These transcription factors are, in turn, thought to control the expression of genes in the output pathways from the oscillator, resulting in behavioural and physiological rhythms.

Adapted from: Bell-pedersen D, Cassone VM, Earnest DJ, Golden SS, Hardin E, Thomas TL, et al. Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nat Rev Genet.* 2005;6(7): 544–56 (66)

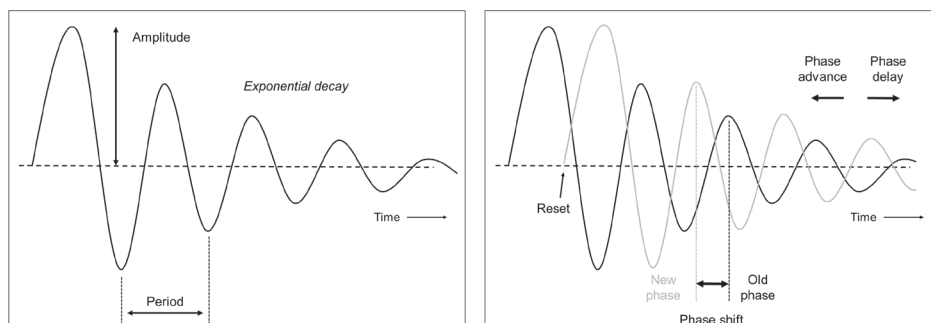


FIGURE 5. Graphical representation of circadian terms relating to cellular gene expression

Circadian rhythms have a cycle length (or period) of about 24 h (left panel). Gene expression oscillates in relation to a mean level and damps over time with decay of amplitudes as individual cells drift out of phase. External input can reset the clock, bringing the oscillators to a synchronous new phase (right).

Adapted from: Liu A, Lewis W, Kay S. Mammalian circadian signaling networks and therapeutic targets. *Nat Chem Biol.* 2007;3(10):630–9 (60)

Light

The circadian system is highly sensitive to environmental light and does not function optimally in the absence of its synchronizing effect. A lack of alternating exposure to bright light and darkness is associated with poor expression of circadian rhythms (reviewed in(68)). Apart from image forming, light also has non-image-forming effects. Light influences timing of sleep and wakefulness when given at certain times of day. Circadian rhythms such as melatonin secretion and the sleep/wake cycle show a phase delay after light exposure early in the subjective night, and a phase advance after early morning exposure. These time dependent effects of light exposure have been expressed in a 'phase response curve' (PRC).(69) These chronotherapeutic effects of light are used in the treatment of psychiatric and certain sleep disorders.(70) However, changes in rhythms do not only result from phase shifts. Sleep improvements may occur without phase shifts. Rather than a phase correction, an increase in the amplitude (increased output of the SCN) appears to be involved. Daytime light has delayed effects during nocturnal sleep, including increased plasma melatonin levels and decreased core body temperature. Daytime light exposure has shown to positively affect nighttime sleep. Use of bright light can ameliorate sleep disturbances in the elderly population.(68) Whole-day bright light exposure improved sleep efficiency and total sleep time in dementia.(71) In younger individuals, bright light during working hours directly improved performance and alertness as well as perceived nighttime sleep quality.(72) The opposite, underexposure to natural light during working

hours correlated with nighttime insomnia and daytime sleepiness complaints.(73) Besides the delayed effects of light, light has some immediate activating effects. When administered either during day or night, it immediately decreases feelings of sleepiness and fatigue.(74,75) Since HD patients often doze off during HD treatment, bright light exposure could hypothetically raise alertness at the time of HD treatment, thereby increasing the build-up of sleep pressure during the day (70), which might facilitate falling asleep at night. Possibly as a result of a strong (circadian amplitude amplifying) light pulse during the day, nighttime sleep might improve as well. Daytime bright light has not been studied yet in patients with ESRD.

Aims and outline of this thesis

The research described in this thesis addresses the relationship between end-stage renal disease of CKD and disturbed circadian rhythms, and investigates possible treatment strategies. A high prevalence of sleep problems in hemodialysis patients, in combination with a demonstrated diminished nocturnal melatonin rise in many of these patients was the starting point of this project on sleep problems and a disturbed circadian clock. In Part I, chapter 2, a review of sleep problems in CKD, diminished melatonin concentrations in ESRD and the effects of short-term melatonin treatment on sleep is given. In addition, effects of melatonin on blood pressure rhythms and oxidative stress are discussed.

The question remains if circadian misalignment really is the underlying mechanism that explains (part of) the sleep problems in ESRD patients. Therefore, we investigated not only the disturbed sleep/wake rhythm and melatonin concentrations in hemodialysis patients, but also focused on the basic molecular clock machinery within peripheral blood cells of these patients. In Part II, chapter 3, we measure circadian rhythms of sleep/wake, melatonin and cortisol and rhythm of clock gene expression in hemodialysis patients' leukocytes. The rhythms of hemodialysis patients are compared with rhythms of healthy volunteers to assess if hemodialysis patients' circadian rhythmicity is lost at three different levels. On the behavioral level, the sleep/wake rhythm is assessed, on the biochemical level the circadian rhythms of the hormones melatonin and cortisol are measured and on the molecular level, the expression of the clock genes *Period 1*, *Period 3*, *Bmal1* and *Rev-Erba* are measured.

In Part III, chapters 4, 5 and 6, the effects of three possible treatment strategies are evaluated. The investigated treatment strategies include an improvement of kidney function with kidney transplantation, the long-term use of exogenous melatonin and light therapy during hemodialysis treatment. Since the incidence and severity of sleep problems



increase with deterioration of kidney function and nocturnal melatonin levels diminish with a decrease in kidney function, we question whether recovery of kidney function can reverse this and accomplish the opposite: improvement of sleep and/or melatonin concentrations. In chapter 4 the effects of kidney transplantation on the sleep/wake rhythm, melatonin levels and 24-h blood pressure rhythms are described. Also the opposite, the effects of a sudden drop in renal function due to unilateral nephrectomy in living kidney donors on circadian rhythms of sleep/wake, melatonin and blood pressure is observed.

Short-term exogenous melatonin administration has shown objective and subjective beneficial effects on sleep onset latency, sleep efficiency and total sleep time in hemodialysis patients.(58) In chapter 5 we study the effects of long-term melatonin treatment on sleep and quality of life in hemodialysis patients. A twelve month treatment of daily administration of 3 mg exogenous melatonin is compared with placebo treatment.

Melatonin and light are both important clock hands of the circadian clock. Melatonin provides important nighttime signals to the body. Light on the other hand, is the strongest daytime cue to the circadian clock. Since the effects of melatonin treatment on sleep have not yet been optimized and light has a substantial influence on circadian rhythmicity, in chapter 6 we explore the effect of bright light-treatment on sleep, daytime sleepiness, melatonin and depressive symptomatology in hemodialysis patients. An overview of the studied treatment strategies is given in figure 6.

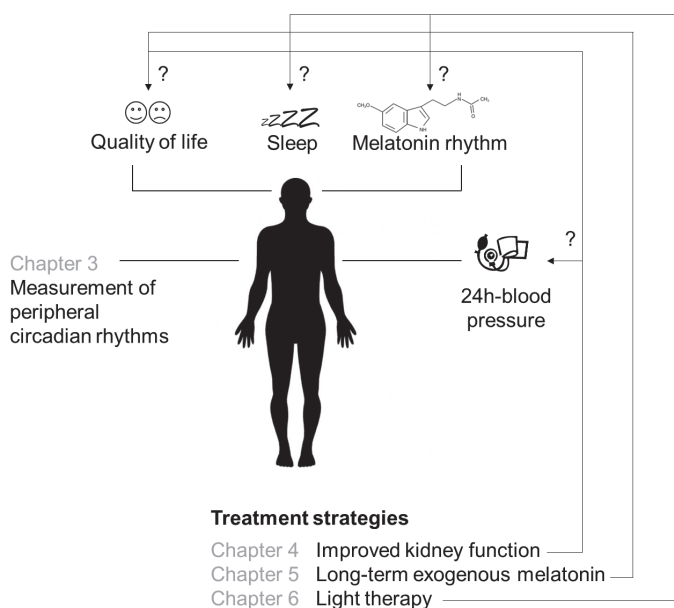


FIGURE 6. Overview of treatment targets studied in this thesis

References

1. Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt K-U, et al. Chronic kidney disease as a global public health problem: approaches and initiatives - a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int.* 2007;72(3):247–59.
2. Kimmel PL, Patel SS. Quality of life in patients with chronic kidney disease: Focus on end-stage renal disease treated with hemodialysis. *Semin Nephrol.* 2006;26:68–79.
3. Parker KP, Kutner NG, Bliwise DL, Bailey JL, Rye DB. Nocturnal sleep, daytime sleepiness, and quality of life in stable patients on hemodialysis. *Health Qual Life Outcomes* 2003;1:68.
4. Iliescu EA, Coo H, McMurray MH, Meers CL, Quinn MM, Singer MA, et al. Quality of sleep and health-related quality of life in haemodialysis patients. *Nephrol Dial Transplant.* 2003;18:126–32.
5. Covic A, Goldsmith DJ. Ambulatory blood pressure monitoring in nephrology: focus on BP variability. *J Nephrol.* 1999;12(4):220–9.
6. Firsov D, Bonny O. Circadian regulation of renal function. *Kidney Int [Internet]. Nature Publishing Group;* 2010;78(7):640–5.
7. Stow LR, Gumz ML. The circadian clock in the kidney.pdf. *J Am Soc Nephrol.* 2011;22:598–604.
8. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl.* 2013;3:19–62.
9. Walker S, Fine A, Kryger MH. Sleep complaints are common in a dialysis unit. *Am J Kidney Dis.* 1995;26(5):751–6.
10. Mucsi I, Molnar MZ, Rethelyi J, Vamos E, Csepanyi G, Tompa G, et al. Sleep disorders and illness intrusiveness in patients on chronic dialysis. *Nephrol Dial Transplant.* 2004;19(7):1815–22.
11. Sabbatini M, Minalé B, Crispo A, Pisani A, Ragosta A, Esposito R, et al. Insomnia in maintenance haemodialysis patients. *Nephrol Dial Transplant.* 2002;17:852–6.
12. Merlino G, Piani A, Dolso P, Adorati M, Cancelli I, Valente M, et al. Sleep disorders in patients with end-stage renal disease undergoing dialysis therapy. *Nephrol Dial Transplant.* 2006;21:184–90.
13. Parker KP, Bliwise DL, Bailey JL, Rye DB. Polysomnographic measures of nocturnal sleep in patients on chronic, intermittent daytime haemodialysis vs those with chronic kidney disease. *Nephrol Dial Transplant.* 2005;20:1422–8.
14. Parker KP. Sleep disturbances in dialysis patients. *Sleep Med Rev.* 2003;7(2):131–43.
15. Dinarello CA. Interleukin-1 and tumor necrosis factor and their naturally occurring antagonists during hemodialysis. *Kidney Int.* 1992;38(Suppl):S68–77.
16. Herbelin A, Nguyen AT, Zingraff J, Ureña P, Descamps-Latscha B. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. *Kidney Int.* 1990;37:116–25.
17. Zaoui P, Hakim RM. The Effects of the Dialysis Membrane on Cytokine Release. *J Am Soc Nephrol.* 1994;4:1711–8.
18. Usvyat LA, Kotanko P, Van Der Sande FM, Kooman JP, Carter M, Leunissen KML, et al. Circadian variations in body temperature during dialysis. *Nephrol Dial Transplant.* 2012;27(3):1139–44.
19. Lack LC, Lushington K. The rhythms of human sleep propensity and core body temperature. *J Sleep Res.* 1996;5:1–11.
20. Lack LC, Gradisar M, Van Someren EJW, Wright HR, Lushington K. The relationship between insomnia and body temperatures. *Sleep Med Rev.* 2008;12(4):307–17.
21. Campbell SS, Dawson D, Zulley J. When the human circadian system is caught napping: evidence for endogenous rhythms close to 24 hours. *Sleep.* 1993;16(7):638–40.
22. Claghorn JL, Mathew RJ, Weinman ML, Hruska N. Daytime sleepiness in depression. *J Clin Psychiatry.* 1981;42(9):342–3.
23. Stapleton S. Etiologies and indicators of powerlessness in persons with end-stage renal disease. In: Miller JF, editor. *Coping with chronic illness: overcoming powerlessness.*



- Philadelphia: F.A. Davis; 1992. p. 163–78.
24. Parker KP, Bliwise DL, Rye DB. Hemodialysis disrupts basic sleep regulatory mechanisms: building hypotheses. *Nurs Res.* 2000;49(6):327–32.
 25. Koch BCP, Wosten YBM, Nagtegaal JE, Kerkhof GA, Wee PM. Prescription of hypnotics and potentially sleep-disturbing medication in haemodialysis patients Objective. *PW Wet Platf.* 2008;2(6):132–5.
 26. Qureshi A, Lee-chiong TJ. Medications and their effects on sleep. *Med Clin North Am.* 2004;88:751–66.
 27. Zoccali C, Mallamaci F, Tripepi G. Sleep apnea in renal patients. *J Am Soc Nephrol.* 2001;12:2854–9.
 28. Novak M, Mendelssohn D, Shapiro CM, Mucsi I. Diagnosis and management of sleep apnea syndrome and restless legs syndrome in dialysis patients. *Semin Dial.* 2006;19(3):210–6.
 29. Monteleone P, Forziati D, Orazzo C, Maj M. Preliminary observations on the suppression of nocturnal plasma melatonin levels by short-term administration of diazepam in humans. *J Pineal Res.* 1989;6(3):253–8.
 30. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ.* 2005;331(7526):1169–75.
 31. McAinsh J, Cruickshank JM. Beta-blockers and central nervous system side effects. *Pharmacol Ther.* 1990;46(2):163–97.
 32. Van den Heuvel CJ, Reid KJ, Dawson D. Effect of atenolol on nocturnal sleep and temperature in young men: reversal by pharmacological doses of melatonin. *Physiol Behav.* 1997;61(6):795–802.
 33. Stoschitzky K, Sakotnik A, Lercher P, Zweiker R, Maier R, Liebmann P, et al. Influence of beta-blockers on melatonin release. *Eur J Clin Pharmacol.* 1999;55:111–5.
 34. Afeche SC, Barbosa R, Scialfa JH, Terra IM, Cassola AC, Cipolla-Neto J. Effects of the blockade of high voltage-activated calcium channels on in vitro pineal melatonin synthesis. *Cell Biochem Funct.* 2006;24(6):499–505.
 35. Kancheva R, Zofkova I, Hill M, Kanchev L. Lack of melatonin response to acute administration of nifedipine and diltiazem in healthy men. *Physiol Res.* 2000;49(Suppl. 1):S119–24.
 36. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis.* 2009;68:1119–24.
 37. Hanly P. Sleep apnea and daytime sleepiness in end-stage renal disease. *Semin Dial.* 2004;17(2):109–14.
 38. Hanly PJ, Gabor JY, Chan C, Pierratos A. Daytime sleepiness in patients with CRF: impact of nocturnal hemodialysis. *Am J Kidney Dis.* 2003;41(2):403–10.
 39. Koch BCP, Nagtegaal JE, Hagen EC, van Dorp WT, Boringa JBS, Kerkhof GA, et al. Subjective sleep efficiency of hemodialysis patients. *Clin Nephrol.* 2008;70(5):411–8.
 40. Unruh ML, Hartunian MG, Chapman MM, Jaber BL. Sleep quality and clinical correlates in patients on maintenance dialysis. *Clin Nephrol.* 2003;59(4):280–8.
 41. Vaziri ND, Oveisi F, Reyes GA, Zhou XJ. Dysregulation of melatonin metabolism in chronic renal insufficiency: role of erythropoietin-deficiency anemia. *Kidney Int.* 1996;50:653–6.
 42. Wide L, Bengtsson C, Birgegård G. Circadian rhythm of erythropoietin in human serum. *Br J Haematol.* 1989;72(1):85–90.
 43. Koopman MG, Koomen GC, Krediet RT, de Moor EA, Hoek FJ, Arisz L. Circadian rhythm of glomerular filtration rate in normal individuals. *Clin Sci.* 1989;77(1):105–11.
 44. Roberts D, Smith DJ. Erythropoietin does not demonstrate circadian rhythm in healthy men. *J Appl Physiol.* 1996;80(3):847–51.
 45. Buemi M, Allegra A, Aloisi C, Mannino G, Trusso S, Vitulo F, et al. The circadian rhythm of erythropoietin in subjects with pre-terminal uremia. *Clin Nephrol.* 1992;37(3):159–60.

46. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. *Sleep Med Rev* 2005;9(1):11–24.
47. Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. Comparisons of the Variability of Three Markers of the Human Circadian Pacemaker. *J Biol Rhythms* 2002;17(2):181–93.
48. Dijk D-J, Cajochen C. Melatonin and the Circadian Regulation of Sleep Initiation, Consolidation, Structure, and the Sleep EEG. *J Biol Rhythms* 1997;12(6):627–35.
49. Lewy AJ, Sack RL. The dim light melatonin onset as marker for circadian phase position. *Chronobiol Int.* 1989;6(1):93–102.
50. Viljoen M, Steyn ME, Van Rensburg BW, Reinach SG. Melatonin in chronic renal failure. *Nephron.* 1992;60(2):138–43.
51. Karasek M, Szufllet A, Chrzanowski W, Zylinska K, Swietoslowski J. Decreased melatonin nocturnal concentrations in hemodialyzed patients. *Neuroendocr Lett.* 2005;26(6):653–6.
52. Karasek M, Szufllet A, Chrzanowski W, Zylinska K, Swietoslowski J. Circadian serum melatonin profiles in patients suffering from chronic renal failure. *Neuroendocr Lett.* 2002;23(suppl 1):97–102.
53. Vaziri ND, Oveisi F, Wierszbiezki M, Shaw V, Sporty LD. Serum melatonin and 6-sulfatoxymelatonin in end-stage renal disease: effect of hemodialysis. *Artif Organs.* 1993;17(9):764–9.
54. Souchet T, Brée F, Baatard R, Fontenaille C, D'Athis P, Tillement JP, et al. Impaired regulation of beta 2-adrenergic receptor density in mononuclear cells during chronic renal failure. *Biochem Pharmacol.* 1986;35(15):2513–9.
55. Ferchland A, Rettkowski O, Ponick K, Deuber HJ, Osten B, Brodde O-E. Effects of uremic plasma on alpha- and beta-adrenoceptor subtypes. *Nephron.* 1998;80:46–50.
56. Plum F, Posner JB. Multifocal, diffuse, and metabolic brain diseases causing stupor or coma. In: Plum F, Posner JB, editors. *The diagnosis of stupor and coma.* Philadelphia: F.A. Davis; 1985. p. 177–303.
57. Holmes EW, Hojvat SA, Kahn SE, Bermes EW. Testicular dysfunction in experimental chronic renal insufficiency: a deficiency of nocturnal pineal N-acetyltransferase activity. *Br J Exp Pathol.* 1989;70:349–56.
58. Koch BCP, Nagtegaal JE, Hagen EC, van der Westerlaken MML, Boringa JBS, Kerkhof G A, et al. The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: a randomized, placebo-controlled, cross-over study (EMSCAP study). *Br J Clin Pharmacol* 2009;67(1):68–75.
59. Ralph MR, Foster RG, Davis FC, Menaker M. Transplanted suprachiasmatic nucleus determines circadian period. *Science* 1990 Feb 23;247(4945):975–8.
60. Liu A, Lewis W, Kay S. Mammalian circadian signaling networks and therapeutic targets. *Nat Chem Biol.* 2007;3(10):630–9.
61. Sadun AA, Schaechter JD, Smith LE. A retinohypothalamic pathway in man: light mediation of circadian rhythms. *Brain Res* 1984 Jun 8;302(2):371–7.
62. Fukuhara C, Tosini G. Peripheral circadian oscillators and their rhythmic regulation. *Front Biosci.* 2003;8:642–51.
63. McNamara P, Seo SB, Rudic RD, Sehgal a, Chakravarti D, FitzGerald G a. Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. *Cell* 2001;105(7):877–89.
64. Challet E, Caldelas I, Graff C, Pévet P. Synchronization of the molecular clockwork by light- and food-related cues in mammals. *Biol Chem.* 2003;384:711–9.
65. Dunlap JC. Molecular bases for circadian clocks. *Cell.* 1999;96:271–90.
66. Bell-pedersen D, Cassone VM, Earnest DJ, Golden SS, Hardin E, Thomas TL, et al. Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nat Rev Genet.*

- 2005;6(7):544–56.
67. Nagoshi E, Saini C, Bauer C, Laroche T, Naef F, Schibler U. Circadian gene expression in individual fibroblasts: Cell-autonomous and self-sustained oscillators pass time to daughter cells. *Cell*. 2004;119:693–705.
 68. Van Someren EJW, Riemersma RF, Swaab DF. Functional plasticity of the circadian timing system in old age: light exposure. *Prog Brain Res*. 2002;138:205–31.
 69. Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase response curve to single bright light pulses in human subjects. *J Physiol* 2003;549(3):945–52.
 70. Wirz-Justice A, Benedetti F, Terman M. Chronotherapeutics for affective disorders. A clinician's manual for light and wake therapy. Basel: Karger; 2009.
 71. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJG, Van Someren EJW. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA* 2008;299(22):2642–55.
 72. Viola AU, James LM, Schlangen LJ, Dijk D-J. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scand J Work Environ Health* 2008;34(4):297–306.
 73. Leger D, Bayon V, Elbaz M, Philip P, Choudat D. Underexposure to light at work and its association to insomnia and sleepiness: a cross-sectional study of 13,296 workers of one transportation company. *J Psychosom Res* 2011;70(1):29–36.
 74. Rüger M, Gordijn MCM, Beersma DGM, de Vries B, Daan S. Time-of-day-dependent effects of bright light exposure on human psychophysiology: comparison of daytime and nighttime exposure. *Am J Physiol Regul Integr Comp Physiol* 2006;290(5):R1413–20.
 75. Cajochen C. Alerting effects of light. *Sleep Med Rev*. 2007;11:453–64.

